27. (New) A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype and a pharmaceutically acceptable excipient, and wherein the vaccine contains approximately 10^8 cell equivalents of each biotype in a volume of 2-5 milliliters.

28. (New) The vaccine of claim 27, wherein at least one *M. bovis* biotype is selected from the group consisting of biotype A, biotype B and biotype C.

REMARKS

Claims 1-21 are pending in this application. New claims 22-28 have been added to more clearly describe and claim the invention. Claims 13-20 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 1-12 and 21 are under examination prior to entry of the new claims added herewith. Claims 1 and 5 have been amended. No new matter is believed added. Support for the amendment of claim 1 can be found throughout the specification as filed, but more specifically on page 8, lines 16-26, more specifically line 21. Support for the amendment to claim 5 can be found in claim 1 and 5 prior to the presently directed amendment of claim 1. Entry of these amendments is respectfully requested.

Support for new claims 22-28 can be found throughout the specification as filed. For example; support for new claim 22 can be found on page 5, lines 28-30; support for new claim 23 can be found in claim 21 and on page 8, lines 16-26, more specifically line 21; support for new claim 24 can be found in original claim 5; support for new claim 25 can be found in claim 1 as amended and at page 5, lines 28-30; support for new claim 26 can be found in Examples 1 and 2 (pages 12-16); support for new claim 27 can be found in original claim 1 and on page 7, lines

11-13 and 23-24; and support for new claim 28 can be found in original claim 5 and on page 7, lines 11-13, and 23-24. Entry of these new claims is respectfully requested.

In light of the following remarks, Applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Rejections under 35 U.S.C.§ 112, first paragraph

Applicants acknowledge the withdrawal of the Rejection of claims under 35 U.S.C. § 112, first paragraph. While indicated in the present Office Action as withdrawing the rejection from claims 5-12, Applicants note that the previous paper Office Action had originally been drafted to indicate that claims 5-12 had been rejected on this basis, but was corrected at the Patent Office prior to transmission to the Applicants to indicate that claims 1-12 were so rejected. As the basis for the rejection of all of claims 1-12 was the same, Applicants believe that this basis of rejection should appropriately have been withdrawn for all of claims 1-12. Confirmation of this withdrawal from all claims under examination is requested for the record.

II. Rejection under 35 U.S.C. § 102

Claims 1-4 and 21 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Howard et al. Specifically, the Office Action alleges that claims 1-4 and 21 drawn to a vaccine composition comprising at least one inactivated or attenuated *M. bovis* biotype and a pharmacologically acceptable excipient are anticipated by a quadrivalent vaccine containing, *inter alia*, killed antigens of *M. bovis*. Further distinctions between what is disclosed by Howard et al. and the present application are indicated as inherent in the vaccines of the prior art. Further, the Examiner emphasizes that it is the Applicants' burden to show a novel or unobvious difference between the claimed product and the prior art. Specifically, the Examiner states that the burden is on the Applicants to show a novel or unobvious difference between the claimed

vaccine and the vaccine of the prior art (i.e., that they do not possess the same material structure and functional characteristics).

Furthermore, the Examiner states that there is "...nothing on the record to show that the claimed vaccine composition is no the same as the vaccine composition of the prior art." Specifically, the Examiner maintains that the "claimed invention is drawn to a vaccine which is protective against Mycoplasma bovis clinical disease in a bovine species comprising at least one inactivated or attenuated Mycoplasma bovis biotype and a pharmaceutically acceptable excipient...[and] there is nothing on the record to show that the claimed vaccine composition is not the same as the vaccine composition of the prior art."

Applicants will specifically address the issue that the vaccine of Howard et al. is not only significantly different from the presently claimed vaccine, but was also different from the vaccine of the present invention as claimed previously prior to entry of the above-directed amendments to the claims. However, prior to doing so, Applicants submit the following comments regarding the amendments and newly added claims. These comments are directed particularly to each of claims 1-4, and 21-28.

In response to the rejection of claims 1-4, Applicants have amended claim 1 to require that the vaccine not include saponin. Support for inclusion or exclusion of saponin in the vaccine of the present invention can be found on page 8, lines 16-26, of the specification as filed. Importantly, Howard et al. includes saponin, particularly it includes Quil A (see Attachment A indicating that Quil A is a saponin). Moreover, Howard et al. states that "...immune responses could be improved for ...the mycoplasmas...by the use of Quil A rather than oil adjuvant (Howard et al., 1987; page 372, second column, starting at the 3rd line). As it is only over the allegedly effective vaccine of Howard et al. that earlier pending claims 1-4 were rejected under

35 U.S.C. § 102(b); Applicants submit that as amended, claims 1-4 are not anticipated and that new claim 23, because it excludes any saponin, is also not anticipated. Applicants therefore request removal of this basis for rejection and allowance of claims 1-4 and 23 to issue.

In respect to claim 21, the Examiner has not withdrawn the rejection despite acknowledgement that "the claim is directed to a vaccine which protects against *M. bovis* mastitis and Heller et al, (1993) and *Bovine Veterinarian*, (2001) provide support for vaccines protecting against bovine mastitis." The Examiner states that "...claim 21 is drawn to a product and limitations such as 'protective against *Mycoplasma bovis* mastitis in a bovine species following systemic administration" are viewed as limitations of intended use."

Applicants take this statement by the Examiner to indicate that the limitation to those vaccines "...protective against *Mycoplasma bovis* mastitis in a bovine species following systemic administration," is considered by the Examiner to be only a limitation of intended use and not a description of the characteristics of the claimed vaccine. Applicants submit that this is an incorrect reading of the claim as written. When read in full, Applicants submit that claim 21 defines a product with the characteristic that it is protective against mastitis. In particular, the limitation does not limit the vaccine's use, as is alleged by the Examiner, but rather limits the claimed vaccine to only those that are protective against *M. bovis* mastitis following systemic administration. It is then, not a limitation of intended use, but rather a limitation directed to the physical characteristics of the vaccine as is reflected in its functional properties. Even if not used for the purpose of preventing *M. bovis* mastitis, the present vaccine claimed is distinguished from the prior art on the basis that if it were to be systemically administered to a bovine species, it would be protective against *M. bovis* mastitis. In other words, it is a clear and precise limitation of the vaccine's composition, albeit not a limitation that uses structural language, but rather one that uses functional language. There is no teaching or even suggestion in Howard et al. that the

composition described has this characteristic. Applicants therefore request withdrawal of this basis of rejection of claim 21 and its allowance to issue.

In respect to new claims 22 and 25-26, each of which require the presence of at least two (2) *M. bovis* biotypes, Applicants submit that these claims are not anticipated by Howard et al. and request that this basis of rejection not be applied to them.

In respect to new claim 24, Applicants submit it is novel and is not anticipated by Howard et al. As acknowledged by the Examiner, Howard et al. does not teach biotypes A, B, and C of *Mycoplasma bovis*. Applicants therefore request that this basis of rejection not be applied to new claim 24.

In respect to new claims 27-28, Applicants submit that both claims are novel and unobvious. Specifically, new claim 27 recites a particular quantity of cell equivalents in a volume of vaccine. Accordingly, claim 27 recites a vaccine having a particular concentration of *M. bovis* cell equivalents as described in the specification on page 7. This particularly recited concentration, i.e., a structural limitation of the present product, distinguishes the present product from the vaccine of Howard et al., which is described as having contained 500 micrograms of protein in approximately 5 mL (see Howard et al., page 373, in section titled "Vaccines"). As outlined in the attached Declaration under 37 C.F.R. § 1.132 by Dr. Marvin F. Field, use of the same methods described in Howard et al. for determining protein concentration reveals that the vaccine of the present invention containing 10^8 cell equivalents corresponds to approximately 0.3 micrograms of *M. bovis* protein. Correspondingly, the doses of vaccine described by Howard et al. contained 1.5×10^{11} cell equivalents dissolved in ~5 mL. In contrast, the vaccine of the present invention, as described in claim 27, contains approximately 10^8 cell equivalents in 2 to 5 mL. Thus, the present vaccine differs from Howard et al. in that it is significantly, i.e., ~500-

1500 fold, more dilute than the vaccine of Howard et al. Consequently, the vaccine of claim 27 is not anticipated by Howard et al. Furthermore, there is nothing in Howard et al. to suggest that a vaccine containing antigen at so much lower a concentration than the composition of Howard et al. would be effective.

New claim 28 depending from claim 27 is further distinguished from the prior art by reciting inclusion of at least one of biotypes A, B or C. As outlined in the attached Declaration under 37 C.F.R. § 1.132 by Dr. Ping Wu, the isolates described in Poumarat et al. are not the same as biotypes A, B and C of the present invention. Thus, biotypes A, B and C were not disclosed by Poumarat et al.

Applicants submit that the previously claimed and presently disclosed vaccine differs from and is not anticipated by the vaccine of Howard et al. The legal basis for this conclusion was laid out in the response to the previous Office action wherein Applicants noted that the *prima facie* case of anticipation can be rebutted by evidence showing that the prior art products do not necessarily have the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. Specifically, Applicants submitted that the "best evidence" for any effectiveness of the quadrivalent vaccine in Howard et al. was insufficient to establish anticipation, because Howard et al. included alternative explanations and did not unequivocally establish that their product necessarily had the same characteristics as the claimed vaccine. In response, the Examiner stated that it is the requirement of the Applicant to show a novel or unobvious difference between the claimed product and the products of the prior art. Applicants take this opportunity to submit further indications that the present vaccine differs from that of Howard et al.

In a first respect, the vaccine as recited in claims 1-4 and 23 differs from that of the prior art in that it does not include any saponin. The vaccine of Howard et al. includes a saponin; specifically, it includes Quil A. Furthermore, inclusion of Quil A is indicated by Howard et al. to be necessary for the level of effectiveness that is possible with the prior art vaccine. As the present vaccine, as demonstrated in the Examples, does not require saponin for effectiveness, the vaccines are not the same.

In a second respect, the vaccine of the present invention is effective at concentrations far below those used by Howard et al. As outlined in the attached 37 C.F.R. § 1.132 Declaration by Dr. Field, a fully effective dose of the present vaccine containing 1×10^8 cell equivalents contains less than 0.5 micrograms of *M. bovis* protein from each biotype included. In contrast, the vaccine of Howard et al., which the Examiner maintains cannot be distinguished from the claimed vaccine, is provided in doses of 500 micrograms for effective vaccination. Applicants submit that a greater effectiveness for a given quantity of an agent can be indicative of a difference in composition.

In a third respect, the vaccine as recited in claims 21-24 differs from that of the prior art in that it is effective against *M. bovis* mastitis. The lack of efficacy of other vaccines in preventing mastitis is reflected in the persistent practices needed to prevent the spread and to mitigate the effects of the disease, as were described in the previous response wherein the Applicants referred to Heller et al. and *Bovine Veterinarian*. In the absence of any disclosure in the literature of an effective vaccine for the prevention of *M. bovis* mastitis, Applicants submit that the present vaccine as presented in claim 21-24 is novel and non-obvious. This effectiveness against mastitis disease distinguishes the present vaccine from other "vaccines" not effective against mastitis.

III. Rejection under 35 U.S.C. § 103

Claims 5-12 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Howard et al. and in view of Poumarat et al. for the reasons set forth in the previous Office action. Specifically, the Office Action alleged that claims 5-12 drawn to the vaccine composition of claim 1, wherein the *M. bovis* bacteria is selected from a group consisting of biotype A, biotype B, biotype C and combinations thereof, is obvious in light of Howard et al. which allegedly teaches vaccines containing *M. bovis* antigens and Poumarat et al. which allegedly teaches the identification of biotypes by use of restriction endonuclease cleavage and gel electrophoresis. Further, the Examiner alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made "to take into account the marked intraspecies genomic heterogeneity among isolates of M. bovis collected from different geographic origins and that antigenic variability must be taken into account in developing diagnostic and vaccination strategies (page 319)." Correspondingly, it is alleged that it would have been *prima facie* obvious to one of ordinary skill in the art to add the *M. bovis* isolates of Poumarat et al. to a vaccine composition according to Howard et al.

The Examiner's position to Applicants' earlier arguments against this basis of rejection is that it fails to account for the teachings of the combination of Howard et al. and Poumarat et al. Specifically, while Howard et al. does not teach biotypes A, B, C of *M. bovis*, it is alleged that Poumarat et al. does teach biotypes. Correspondingly, the Examiner asserts that one of skill in the art would be motivated to add the *M. bovis* biotypes to the vaccine of Howard et al. and that one of skill in the art would have expected that a vaccine comprising multiple biotypes would be highly protective in providing protection against *M. bovis* infections. Finally, the Examiner asserts that limitations such as that in claim 21 stating that the vaccine is "protective against

Mycoplasma bovis mastitis in a bovine species following systemic administration" are viewed as limitations of intended use.

In response, Applicants submit that the Examiner has not fully considered the teachings of Poumarat et al; specifically, the teachings on page 318, in the first and second full paragraphs of the page. In the first full paragraph, the authors describe that "[t]here appeared to be *no relation* between the genomic variability of *M. bovis* and the antigenic variability" (emphasis added). In the second full paragraph, the apparent lack of antigenic variation is emphasized when the authors state that "*M. bovis*...appears to exhibit a global antigenicity that is fairly homogenous." Poumarat et al. do note, however, that this lack of antigenic variation, along with the protein patterns are described to "...appear to be in contradiction with the great variability of antigenic patterns revealed by immunoblotting." In brief, the "biotyping" in Poumarat et al. on which the Examiner relies does not appear to correlate with any difference in immunoreactivity or with strain identity. If, as is stated by Poumarat et al. in the first full paragraph of page 318, "[a]ntigenic profiles of the *M. bovis* strains differed markedly one from another, the difference being equally great among strains belonging to the same genomic group and those coming from different genomic groups," then how can the restriction endonuclease analysis described be considered "biotyping" as is described in the present application? Applicants submit that it cannot be and would not have been prior to the present application.

Further, this work appears to establish that genotypic analysis is not suitable for use in "typing" *M. bovis* even though it does appear to work for other pathogens (see Poumarat et al, p. 318, 1st full paragraph). Correspondingly, Applicants submit that even if the use of immunoblotting in Poumarat et al. can be argued to establish a teaching for multiple "biotypes" and for "biotyping" (i.e., by use of immunoblotting), there is no support for a gene- or nucleic acid sequence-based biotyping method as is taught in the present application. Consequently, as

there is not necessarily a correlation between the nucleic acid based analysis taught in Poumarat et al. and an *M. bovis* strain's immunoreactivity, Applicants submit that Poumarat et al. cannot render obvious a vaccine such as new claim 26 wherein the biotypes can be distinguished from one another by PCR fingerprinting.

Still further, Applicants submit that Poumarat et al. does not render obvious the present invention as claimed in claims 5-7, 12, 24, and 28 wherein at least one of the *M. bovis* biotypes is selected from the group consisting of biotype A, biotype B and biotype C. Poumarat et al. provides no guidance as to the specific biotypes A, B, or C. Specifically, these biotypes provided by the present invention differ from those described in Poumarat et al. as shown in the attached 37 C.F.R. § 1.132 Declaration by Dr. Ping Wu. More specifically, the Declaration describes the Restriction Endonuclease Analysis (REA) of four isolates of *M. bovis* that include members of biotypes A, B and C. The REA was done in accordance to the method described by Poumarat et al. using the same restriction endonucleases and the results were compared to those published in Poumarat et al. On the basis of this comparison, it is concluded that the isolates identified and characterized in Poumarat et al. differ from biotypes A, B and C. If biotypes A, B, and C differ from particular strains identified by Poumarat et al., a combination of Poumarat et al. and Howard et al. cannot suggest the present invention as the combination of references does not suggest a vaccine that comprises any one of the undisclosed biotypes A, B or C. Accordingly, the combination of Poumarat et al. with Howard et al. cannot provide the invention as claimed in claims 5-7, 12, 24, and 28.

Each of the above-outlined problems with the Office action's finding of obviousness demonstrates why rejection of the claims is inappropriate. Specifically, the three basic criteria of a *prima facie* case of obviousness for claims 5-12 and 21-28, namely; (1) some suggestion or motivation to combine reference teachings; (2) a reasonable expectation of success; and (3) the

combination of references must teach or suggest all claim limitations, can not be met by a combination of Howard et al. and Poumarat et al.

More specifically, in regard to the first criterion, Applicants maintain that Howard et al. does not provide a vaccine protective against *M. bovis* disease in general, or more particularly, against *M. bovis* mastitis and correspondingly, there can be no motivation to modify Howard et al. with the teachings of Poumarat et al. to provide the present invention. Further, as outlined more clearly above, Poumarat et al. does not teach any recognizable relationship between the determinable characteristics of strains of *M. bovis* and their immunogenicity besides immunogenic reactivity itself. Accordingly, Applicants submit that Poumarat et al. cannot render obvious any of the presently claimed inventions that rely upon or include biotypes or biotyping as determined by genetic or nucleic-acid based techniques. This includes each of the biotypes A, B and C. Finally, because biotypes A, B, and C are not strains identified by Poumarat et al. (see attached Declaration by Dr. Ping Wu) and the teachings of Poumarat et al. itself are that genetic based techniques are not reliable indicators of antigenic differences, Poumarat et al. does not teach the modification of any composition on the basis of nucleic acid based techniques. Consequently, the presently claimed invention that recites the inclusion of biotypes A, B, or C also cannot be rendered obvious as Howard et al. cannot be modified by the teachings of Poumarat et al. to provide the present invention if Poumarat et al. cannot distinguish or recognize or identify the present biotypes.

More specifically in regard to the second criterion, Howard et al. and Poumarat et al. cannot provide a reasonable expectation of success. As outlined above, Poumarat et al. teaches that "[t]here appeared to be no relation between the genomic variability of *M. bovis* and the antigenic variability." Applicants submit that attempts to biotype variants using genetic or nucleic acid based techniques, or to use biotypes A, B, and C characterized by the use of a

nucleic acid based technique, could not be considered to have a reasonable expectation of success in light of the teaching of Poumarat et al. Accordingly, combination of Poumarat et al. with Howard et al. cannot be a proper basis for obviousness for claims 5-12, 24, 26, and 28 which all require the inclusion of biotypes A, B or C or use of nucleic acid-based biotyping. Particularly, as biotypes A, B and C are not provided by Poumarat et al., Howard et al. can not be modified by the teaching of Poumarat et al. to provide any claim that specifically recites the inclusion of biotypes A, B or C with any expectation of success.

More specifically in regard to the third criterion, Howard et al. and Poumarat et al. can not teach or suggest all claim limitations. Specifically, the combination cannot provide any claim limitation that requires the inclusion of any one of biotypes A, B or C as neither reference provides the specified biotype. Accordingly, they cannot render claims 5-8, 12, 24 or 28 obvious. Further, the combination cannot provide any limitation as to the effectiveness of the vaccine "against *Mycoplasma bovis* mastitis in a bovine species following systemic administration" as is required in claims 21-24. This limitation, as outlined above in Section II., is not a limitation of intended use, but is rather a clear limitation as to the composition and characteristics of the claimed vaccine that distinguish it from the prior art.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

Credit Card Payment Form PTO-2038 authorizing payment in the amount of $767.00, representing $147.00 for the fee for additional claims, $460.00 for a three month Extension of Time, and $160.00 for filing a Notice of Appeal (small entity), are enclosed. This amount is

believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No.14-0629.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Box AF, Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Gwendolyn D. Spratt — 12-18-02

Gwendolyn D. Spratt — Date

Version with Markings to Show Changes Made

In the claims

1. (Amended) A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype and a pharmaceutically acceptable excipient, and wherein the vaccine does not include saponin.

5. (Amended) A vaccine which is protective against *Mycoplasma bovis* clinical disease in a bovine species comprising at least one inactivated or attenuated *Mycoplasma bovis* biotype and a pharmaceutically acceptable excipient [The vaccine of claim 1], wherein at least one of the inactivated or attenuated *Mycoplasma bovis* biotypes is selected from the group consisting of biotype A, biotype B and biotype C.